Remarks

Claims 1, 16, 20-24, 26, 27 and 31-35 are pending. Claims 4, 25, 28 and 29 have been cancelled. Claims 1, 26 and 27 have been amended. New Claim 35 has been added. Support for the amendments may be found throughout the specification as filed and, for example, for new Claim 35 at page 24, lines 4 to 6. The Applicants respectfully request entry of the amendments which are believed to place the application in condition for allowance.

Additionally, the Applicants note that a Supplemental Information Disclosure Statement has been submitted with this Response.

Claims 1, 16, 20-24, 26, 27 and 31-32 are rejected under 35 USC §112, first paragraph, as failing to comply with the written description requirement. The rejection refers to the requirement for an alteration in the metalloproteinase balance and states that it is not clear from the specification whether (i) binding between beta 1 integrin and the MMPs occurs via the claimed TAEKLK residues and (ii) the claimed antibodies would act as MMP inhibitors and/or activators in order to promote tissue repair. The rejection further states that the specification fails to disclose whether binding of beta 1 integrin via TAEKLK to MMP2 and MMP9 leads to their activation or inhibition.

The Applicants respectfully disagree. Claim 1 recites that the anti-TAEKLK antibody modulates function of beta 1 integrin resulting in (i) an inhibition of the apoptotic pathway, (ii) an alteration in the metalloproteinase balance and (iii) an increase in the anabolism of the extracellular matrix. The Applicants respectfully submit that one skilled in the art would understand from the specification that the binding between beta 1 integrin and the MMPs does not occur via the claimed TAEKLK residues because no known MMP has been reported or found to bind the TAEKLK residues. Instead, one skilled in the art would understand that the interaction of MMPs with beta1 integrin is through binding to beta 1 integrin's partnering alpha chain or other co-receptors, such as plasminogen receptors. The effect on MMP activity is mediated by the functional modulation of beta1 integrin by the claimed antibodies.

Moreover, the Applicants respectfully submit that one skilled in the art would understand from the specification that it is an alteration in MMP balance which results in tissue repair in the Applicants' method, rather than the inhibition and/or activation of one or more specific MMPs.

By way of background, MMPs are synthesized and secreted in a latent form which is enzymatically inactive (proMMP) and which requires extracellular activation. The proMMPs can be

activated by many mechanisms including activation by other proteases (Shapiro et al., 1995). An increase in the activity of any given MMP does not decide the outcome as the outcome will also depend on, for example, the level of inhibitors present, the levels of other MMPs which could be activated by the first MMP and which could, in turn, activate other MMPs, and, further, the timing of activation of the MMP. The phasic nature of MMPs/TIMPs in active remodelling has been highlighted in various tissues, as shown by Wang and Tsirka (2005) and Zhao et al. (2006). In both of these reports, it was clearly shown that the beneficial effect of the inhibition of MMPs was dependent on the timing post injury of the MMP inhibition. With regard to Corey et al., the investigators focused on a single MMP9 in transgenically altered animals. There was no description of the effect of genetic deletion of MMP9 on other MMPs or indeed on inhibitors of MMPs (TIMPs). The Applicants submit that it is MMP balance, rather than absolute activity or inhibition, which is key in tissue repair.

The Applicants respectfully submit that there are detailed descriptions in clinical research literature showing the importance of MMP/TIMP balance. As an example, the Applicants refer to the study by Lim et al. (2000) relating to the role of MMP/TIMP balance in emphysema. This study looked at the effect of smoking on the release of MMP9 and its inhibitor TIMP1 from alveolar macrophages. The alveolar macrophages were obtained from bronchoalveolar lavage of eleven smokers and eleven nonsmokers which were cultured in the presence of control medium, IL-1beta and lipopolysaccharide. Airway macrophages from smokers released greater amounts of both MMP9 and TIMP1 without any stimulation and in response to IL-1beta and lipopolysaccharide than did those of non-smokers. Their conclusion was that the release of proteases and antiproteases by airway macrophages is increased in cigarette smokers.

The rejection further states that the specification fails to show that anti-TAEKLK antibodies lead to modulation in the MMP balance. In response, the Applicants submit that anti-TAEKLK antibodies lead to modulation in the MMP balance and this is supported by the attached Declaration under 37 CFR §1.132 of Dr. Rehab Al-Jamal, one of the inventors of the claimed subject matter. This Declaration includes experimental data (Appendix A) showing that targeting the TAEKLK amino acid residues of beta1 integrin using the JB1a antibody had an effect on MMP12 levels in emphysematous mice and also had an effect on MMP2, 9 and 12 levels in emphysematous adult human lung fibroblasts.

The rejection further states that the Applicants have pointed to well known clones that bind to the TAEKLK sequence of beta 1 integrin, such as SG/7, SG/19, C30B and D11B, but that none of the taught clones are shown to cause alteration in MMP balance. In response, the Applicants respectfully bring Saito et al. (2010) and Tsuji et al. (2002) to the Examiner's attention. The Applicants respectfully submit that these documents describe the effect of SG/19 on MMP9 activity. The Applicants therefore submit that the effect of anti-TAEKLK antibodies on modulation of the MMP balance has been shown.

Furthermore, the rejection states that the specification does not provide a genus of anti-beta 1 integrin antibodies that bind TAEKLK and result in functional modulation of beta 1 integrin leading to an alteration in the MMP balance. The rejection states that there does not appear to be an adequate description in the specification as filed of the essential structural feature that provides the recited function of modulation in the metalloproteinase balance that would lead to promotion of tissue repair. The Applicants respectfully disagree and submit that the specification discloses an anti-beta 1 integrin antibody that binds TAEKLK and it has been shown that such antibodies alter the MMP balance as discussed above. The Applicants therefore submit that, as would be known to those skilled in the art, raising another clone to the TAEKLK sequence of beta 1 integrin will replicate the observed effects of JB1a binding and result in modulation of the MMP balance and tissue repair. In providing the sequence of beta 1 integrin to which the antibody must bind in order to achieve the modulation of the MMP balance and tissue repair, the Applicants submit that the specification as filed therefore provides an adequate description of the essential structural feature that provides the recited function of modulation in the metalloproteinase balance leading to promotion of tissue repair.

As detailed in the Applicants' response to the Office Action dated January 28, 2010, the JB1a antibody was the sole clone known to bind the TAEKLK amino acid residues which was available commercially at the time of filing the application. Other clones which are known to bind to the same sequences, as quoted in the review by Al-Jamal and Harrison, are SG/7 and SG/19, which were developed by Miyake et al., and the clones C30B and D11B developed by Ni and Wilkins. The D11B and C30B were not retrievable from the cell banks as viability was lost. As noted above, the effect of SG/19 on MMP9's activity has been described (Saito et al., 2010 and Tsuji et al., 2002). However, the epitope of SG/19 on beta1 integrin was not reported until 2004 (Luo et al., 2004). The published work of Luo et al. shows that clone SG/19 induces an intermediate conformational state of

beta 1 integrin similar to that induced by JB1a, as evidenced by the inventors' FRET data for JB1a submitted in the response to the Official Action dated July 28, 2009. Other clones, such as 6S6 and TS2/16, have been shown to target beta1 integrin by sequences other that the TAEKLK sequence. The 6S6 epitope is estimated to be within the EGF repeat of the extracellular domain of beta1 integrin and TS2/16 targets the 207-218 amino acid residues within the beta A domain. Neither antibody produced the same effect as targeting the TAEKLK amino acid residues and both failed to show any effect on MMP balance. The Applicants therefore submit that the targeting of the TAEKLK sequence of beta 1 integrin is the essential structural feature that provides the recited function of modulation in the metalloproteinase balance leading to promotion of tissue repair.

The Applicants therefore submit that the specification describes the claimed subject matter in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of that claimed subject matter. The Applicants respectfully request withdrawal of the written description rejection.

Claims 1, 16, 20-24, 26, 27 and 31-32 are rejected under 35 USC §112, first paragraph, as non-enabled. The rejection states that Corry et al. teaches that inactivation of MMP9 leads to airway hyperresponsiveness, mucin and glycoprotein hypersecretion and elevated serum IgE levels. The rejection further states that those skilled in the art would not know which MMP is involved in promoting tissue repair and whether an increase or decrease in the specific MMP would result in tissue repair.

The Applicants respectfully disagree. The Applicants refer to the discussion provided above relating to MMP balance and submit that it is an alteration in MMP balance which results in tissue repair in the Applicants' method rather than the inhibition and/or activation of one or more specific MMPs. An increase in the activity of any given MMP does not decide the outcome as the outcome will also depend on, for example, the level of inhibitors present, the levels of other MMPs which could be activated by the first MMP and which could, in turn, activate other MMPs, and, further, the timing of activation of the MMP. With regard to Corey et al., the investigators focused on a single MMP9 in transgenically altered animals. There was no description of the effect of genetic deletion of MMP9 on other MMPs or indeed on inhibitors of MMPs (TIMPs). The Applicants submit that those skilled in the art would be aware that it is MMP balance rather than absolute activity or inhibition which is key in tissue repair.

The Applicants have shown that administering an antibody which binds in a region comprising TAEKLK to a tissue wherein extracellular matrix of the tissue has been degraded leads to an alteration in MMP balance resulting in tissue repair. Those skilled in the art would be able to produce an antibody which binds to this region without undue experimentation. Furthermore, those skilled in the art would have no difficulty in confirming the presence of beta 1 integrin modulating activity which results in functional modulation of beta 1 integrin leading to (i) an inhibition of the apoptotic pathway, (ii) an alteration in the metalloproteinase balance and (iii) an increase in the anabolism of the extracellular matrix. For example, page 35, line 20 to page 36, line 2 of the application as filed provides guidance as to how functional modulation of beta 1 integrin may be assessed, for example, by assessing the effect of the antibody on apoptosis using apoptosis assays which would be known to those skilled in the art. One skilled in the art would therefore have no difficulty in carrying out the method of Claim 1.

The rejection concedes that the Applicants have provided working examples for emphysema, Parkinson's disease, arthritis and Alzheimer's, but alleges these are not representative of the whole genus of tissue repair wherein extracellular matrix of the tissue has been degraded. The rejection states that the Applicants' examples are insufficient to show that the claimed methods can be extrapolated to the claimed types of tissue repair and tissue injury wherein the extracellular matrix is degraded.

However, the rejection concedes that the specification is enabled for tissue repair in the treatment of chronic obstructive pulmonary diseases (COPD). The Applicants submit that interstitial lung diseases such as COPD affect the inflammation state and oxygen level at a basic level and this has a resultant effect in every cell in every tissue. In particular, COPD is characterized clinically by the development of poorly reversible and progressive airflow limitation and the presence of exacerbations characterized by uncontrollable inflammation which is not responsive to any available steroids and non-steroidal anti-inflammatories. This inflammation is not restricted to the lung as the inflammatory mediators can be found in the systemic circulation and thus can affect all tissues.

The lung is highly vascularized and, thus, even MMPs and other mediators can spill over into the systemic circulation. There has been past evidence of the lack of compartmentalization of injury in the lung from studies on ventilator induced lung injury (Murphy et al., 2000; Tremblay et al., 1997). These showed ventilation of rabbits with a double lumen endotracheal tubing to deliver two

different ventilation volumes to either lung; to one lung a high volume tidal ventilation was delivered to induce mechanical injury and to the other lung a normal tidal ventilation was delivered. In this study the investigators were able to clearly show that the inflammatory burst resulting from the injurious ventilation was evident in the normally ventilated lung. Similar findings are reported in unilateral arthritis models where inflammation and swelling is seen in the contralateral joints even when not injected with the injurious agents.

Furthermore, the oxygen level in the blood (PO2) in COPD is often reduced as a result of the airway obstruction and the destruction in the lung parenchymal structure leading to a reduction in the gas exchange surface area. The lowering of oxygen levels in the systemic circulation will affect all body tissues. There have been reports documenting the association of COPD with cognitive function decline (dementias) (Hung et al., 2009; Kozora et al., 1999; Ortapamuk & Naldoken, 2006), restless leg syndrome (Lo Coco et al., 2009), cardiovascular diseases (Chaouat et al., 2008) and arthritis (Bongartz et al, 2010). Restless leg syndrome is caused by dopaminergic neuronal damage in the substantia nigra, as that seen in Parkinson's disease. Frequently drugs developed for Parkinson's disease which target dopamine are marketed under a label for use in restless leg syndrome.

In view of the lack of compartmentalization of injury in the lung and the effect of COPD on all tissues and the known association between COPD and other conditions, the Applicants respectfully submit that the claimed methods can be extrapolated to the repair of all tissue types wherein the extracellular matrix is degraded.

In view of the above, the Applicants submit that one of ordinary skill in the art can readily carry out the method of the claimed subject matter without undue experimentation. The Applicants respectfully request withdrawal of the enablement rejection.

Claims 1, 16, 20-24 and 31-32 are rejected under 35 USC §102(b) as being anticipated by US Patent Publication No. 2003/0109435 (US '435), as evidenced by the by Al-Jamal and Chemicon International catalog no. MAB1965.

The Applicants respectfully submit that US '435 fails to teach all of the elements of Claim 1 as amended. It does not teach administration of an antibody, which binds to the beta 1 integrin molecule in a region of amino acid residues 82 to 87, to a tissue wherein extracellular matrix of the tissue has been degraded. Paragraph [0016] of US '435 states that the invention provides methods of inhibiting formation of an amyloid deposit. Paragraph [0199] states that antibodies to the beta 1

integrin subunit inhibit formation of extracellular meshworks of amyloid proteins. Thus, US '435 clearly teaches that the antibody is administered before degradation of the extracellular matrix in order to inhibit fibril formation. This differs from the claimed method of the present application wherein the antibody is administered following degradation of the extracellular matrix in order to promote tissue repair.

The Applicants submit that the protective effect observed on administration of the antibody in US '435 was not because of inhibition of interaction with degraded extracellular matrix, but rather inhibition of extracellular fibril formation. In paragraph [0312] of US '435, it is taught that fibronection and meshworked fibronectin both protected from amyloid toxicity. This indicates that matrix degradation was not the mode for the inhibition of toxicity. This is even more evident by the lack of protective effect reported in US '435 when using laminin in its native form, though antibodies against laminin itself did protect from injury. The Applicants therefore submit that US '435 does not teach administration of the antibody to a tissue wherein extracellular matrix of the tissue has been degraded.

The Applicants respectfully request withdrawal of the rejection made in view of US '435.

Claims 1, 16 and 20-24 are rejected under 35 USC §102(b) as being anticipated by US Patent No. 6,123,941 (US '941).

The Applicants respectfully submit that US '941 fails to teach all of the elements of Claim 1. It does not disclose administering an antibody to a tissue wherein extracellular matrix of the tissue has been degraded. Rather, US '941 teaches administering an antibody to tumor cells. The Applicants submit that tumor cells do not constitute cells wherein extracellular matrix has been degraded.

Malignant transformation is the process by which cells are genetically altered due to exposure to radiation or carcinogenic chemicals or the acquisition of foreign DNA from organisms such as viruses. The resultant cells become immortalized due to the loss of cell cycle checks caused by mutations of various proteins such as proto-oncogenes (e.g. p53). In other words, the cells can avoid the normal cell life cycle and are highly active in cell division and in all the processes which cell divisions entails, including increased extracellular and intracellular protein synthesis. Thus, in tumor tissue synthesis of extracellular matrix of the tissue is increased and cells can evade cell death. In contrast, tissue injury wherein the extracellular matrix is degraded entails degradation of

extracellular matrix and loss of survival cues by the cell leading to cell death and loss of tissues. The Applicants therefore submit that there is a clear difference between tissues wherein extracellular matrix of the tissue has been degraded leading to cell death and tumor tissues wherein synthesis of extracellular matrix is increased and cell death is evaded.

The Applicants respectfully submit that US '941 teaches administration of the antibody to reverse the malignant phenotype in cells, thus reducing cell division and reinstituting the normal cell cycle wherein the cells can die naturally. In the Applicants' claimed method, administration of the antibody results in an inhibition of the apoptotic pathway, thus preventing cell death during degenerative injury wherein the cells would otherwise die.

The rejection states that in US '941 T4 cells revert to normal phenotype when beta 1 integrin function-blocking antibody is applied, but normal cells die as a result of application of the beta 1 integrin function-blocking antibody and the level of response varies as a function of the concentration of applied antibody such that it is important to use the correct concentration to balance these two effects. The Applicants submit that to those skilled in pharmacology, this statement regarding the dependency of the pro-apoptotic effect on dose indicates that saturation of binding sites with the antibody was incomplete. Dosage is usually determined by the number of binding sites. In tumors, there have been recent reports where the level of beta1 integrin is increased in addition to its glycosylation. Therefore, it would be clear to those skilled in the art that the doses used in US '941 would be relatively higher than those used in normal non-transformed tissues.

Inhibition of beta1 integrin in normal cells is known to induce detachment-induced cell death or anoikis (a form of apoptosis). The Applicants' claimed method does not relate to inhibition of the beta 1 integrin antibody as the more potent inhibitor clone 6S6 failed to produce similar effects to those shown by JB1a. Thus, inhibition of beta 1 integrin is not sufficient to explain the effects presented in Table III of US '941 wherein the efficacy of JB1a is statistically significant from that disclosed from targeting using clone AIIB2 in a comparable ascites formulation (based on the disclosed mean and SEM assuming the values are from at least 3 independent measurements). AIIB2 is known to those skilled in the art as a potent inhibitor similar to clone 6S6.

The Applicants respectfully request withdrawal of the rejection made in view of US '941.

Claims 1 and 20 stand rejected under 35 USC §103(a) as being obvious over US '941 in view of Owens et al.

The deficiencies of US '941 are discussed above. Owens et al. does not remedy these deficiencies. The Applicants therefore respectfully request withdrawal of the rejection made in view of US '941 and Owens et al.

Claims 1, 16, and 20-24, 26, 27 and 31-34 stand provisionally rejected on the ground of nonstatutory double patenting over Claims 1, 2, 5, 11, 16, 19, 24, 25, 32, 35, 57 and 59-63 of copending US Application No. 12/528,749. The Applicants respectfully submit that because the rejection is provisional, they will address it when the rejection becomes non-provisional.

In light of the foregoing, the Applicants respectfully submit that the entire application is now in condition for allowance, which is respectfully requesied.

Respectfully submitted,

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